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Case Reports

LEVARTERENOL (LEVOPHED) THERAPY IN ACUTE MYOCARDIAL INFARCTION (INCLUDING CASE REPORT OF RECOVERY FOLLOWING UNUSUALLY HIGH CONCENTRATION)

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LEVARTERENOL (aminoethanol catechol), also known as Levophed, l-nor-adrenaline and l-norepinephrine, was first synthesized in 1904. It is a sympathomimetic primary amine which has been found in blood, urine, adrenal medulla and particularly in phæochromocytoma. There is no longer any doubt that this vasopressor amine has saved the lives of many patients, especially following severe myocardial infarction[3-5] complicated by acute hypotension. The latter is due to the inability of the left heart to maintain an adequate output (cardiogenic shock), and is not rare after an acute myocardial infarction. If not quickly reversed, the condition results in a mortality rate of 80% or higher.[2] Levophed has been shown to combat this condition better than any other therapy, such as retrograde arterial infusions or cortisone administration, and is more effective than any other vasopressor drug.[2] It slows the pulse rate and increases total peripheral resistance by causing generalized vasoconstriction of arteries, capillaries and veins (although it produces coronary vasodilatation[7]). Thus the blood pressure is elevated and the mean aortic pressure rises, producing a proportionate increase of coronary flow with minimal side-effects such as severe arrhythmias. At the same time it produces a decrease in renal plasma flow[6] and a rise in the filtration fraction owing to efferent glomerular arteriolar constriction. It does not produce central nervous system stimulation and tachycardia with the associated anxiety, discomfort and peculiar feelings that follow epinephrine (adrenaline) administration. It is also eight times less toxic. Because of the increase in pulmonary arterial, capillary and venous pressures, the possibility of aggravating or producing pulmonary œdema must be considered, especially in those patients already in congestive heart failure.

The usual response is exemplified in the series of Miller *et al.*[5] Out of nine patients with shock accompanying acute myocardial infarction, five ultimately survived. Without levarterenol no more than two would have recovered. In Kurland and Malach's[3] series of 14 patients there were only four survivals, in spite of the fact that there was a temporary satisfactory pressor response in 12 of 17 courses of treatment. It is noted that in this series the concentration of levarterenol was not increased beyond one ampoule per 1,000 c.c. of infusion (4 micrograms per c.c.). Griffith *et al.*[2] controlled shock in 17 out of 30 patients, using two ampoules of levarterenol per 1,000 c.c. They defined shock as a condition of marked hypotension lasting for an hour or longer, and accompanied by signs of peripheral circulatory collapse. In a patient whose blood pressure had previously been within normal limits, a systolic blood pressure reading of 80 mm. Hg or below was accepted as evidence of shock. A formerly hypertensive patient with a systolic blood pressure of 100 mm. Hg or below was considered to be in shock.

METHOD OF ADMINISTRATION

The levarterenol (Levophed) solutions are prepared by adding 4 c.c. (1 ampoule) levarterenol bitartrate 0.2% (equals 0.1% base) to 1,000 c.c. of 5% dextrose in distilled water, the resultant solution containing 4 mcg. base (8 mcg. bitartrate) per c.c. It has been recommended that if the shock has lasted between one and three hours, showing no response to the usual measures, particularly oxygen and morphine, infusion should begin at 10 drops per minute but should increase to 80 drops per minute if necessary to keep systolic blood pressure over 100 mm. Hg (over 120 if the patient had been hypertensive). In order to limit the total amount of fluid administered, or if blood pressure rise is insufficient, one may according to the recommendations in the literature gradually increase the concentration as much as four times. The highest concentration reported[5] (with recovery) is 100 drops per minute of a solution containing 32 mcg. of levarterenol bitartrate per c.c. (4 ampoules per 1,000 c.c. diluent). The object of this therapy is of course to adjust the rate of flow to

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TABLE I.

SUMMARY OF CASE HISTORY
MRS. M.B., AGED 62 YEARS—ADMITTED JUNE 4, 1955

Date	*Condition of patient*	*Amount of Levophed (per 1,000 c.c. 5% dextrose)*	*Other therapy*	*Other findings*
June 4, 1955	Onset of heart attack, acutely ill.	1 ampoule at 6 to 8 drops per min.	Oxygen, morphine, dicoumarol.	ECG showed extensive cardiac infarct
June 6, 1955	Right and left heart failure; cyanosis, orthopnœa.	As above.	Digitalization, thiomerin, low salt diet.	WBC 14,250 Hb. 84%. Sed. rate 23 mm./hr.
June 8, 1955	Heart failure improving.	4 ampoules at 40 to 60 drops per min.	1,200 calorie diet.	
June 9, 1955	Recurrent hypotension.	5 ampoules at 30 to 60 drops per min.		
June 11, 1955	Recurrent hypotension.	6 ampoules at 40 to 60 drops per min.		
June 15, 1955	Peripheral vascular collapse.	7 ampoules at 50 to 60 drops per min.		
June 18, 1955	Much better.	1 ampoule at 30 drops per min.		
June 23, 1955		1 ampoule at 4 to 8 drops per min.		
June 24, 1955		Discontinued.	2,000 c.c. 5% dextrose in distilled water.	
June 27, 1955	Oxygen no longer necessary.			
July 24, 1955	Out of bed.			Sed. rate and WBC normal.
Aug. 3, 1955	Able to walk length of corridor; discharged.		Dicoumarol stopped.	
April 1956	Able to do her own housework, etc.		Digoxin 0.25 mg. daily, occasional thiomerin.	

hold the blood pressure at the desired level with the minimum rate of administration. The rate of infusion is gradually reduced (and eventually stopped) over a variable period, depending on when the blood pressure maintains itself.

CASE HISTORY* (See Table I)

Mrs. M.B., a 62-year-old white woman, was admitted to the medical ward of the Northwestern General Hospital on June 4, 1955, suffering from severe, squeezing, substernal chest pain which had come on suddenly, lasted three to four hours and was associated with shortness of breath.

Except for the usual reduction in exercise tolerance in a woman of her age and weight, there had been no cardiovascular symptoms nor was there a history of any previous cardiovascular disease or any other significant past illness. There was no diabetes or high blood pressure but she had been overweight for many years.

On admission the patient appeared pale and in distress because of severe chest pain and slight orthopnœa but there was no increased distension of neck veins. Her pulse was feeble and blood pressure 108/80 mm. Hg, with a cardiac rate of 92 per minute and regular. Heart sounds were faint and of poor quality. No significant murmurs or rub were audible. Except for moderate obesity, the remainder of the general physical examination was not remarkable. Her chest was clear, and liver was not palpable or tender. No œdema of ankles or sacrum was present. Ophthalmoscopy revealed slight tortuosity of retinal vessels but no AV nicking or hæmorrhages, exudates or papilloedema. She was immediately placed in an oxygen tent and dicoumarol therapy instituted; morphine sulphate grain ¼ subcutaneously was given three times during the first four hours after admission (to control the pain).

One hour after admission, the patient's blood pressure had fallen to 85/70 mm. Hg while the cardiac rate had risen to 110 per minute. Her pulse became very weak and thready and she appeared to be in extremis. In view of the fact that the blood pressure had remained down for one hour in spite of the above therapy, levarterenol was started. Within a few minutes of beginning the infusion the blood pressure rose to 110/90 mm. Hg and was maintained in that neighbourhood by 1 ampoule* of levarterenol at a rate of 6 to 8 drops per minute.

*Prepared with the assistance of Dr. A. W. Brickenden, Attending Physician, Northwestern General Hospital, Toronto.

*Throughout the history each ampoule refers to 4 c.c. of levarterenol in 1,000 c.c. of 5% intravenous dextrose in distilled water. "Maintenance of blood pressure" means prevention of drop below 100 mm. Hg systolic pressure.

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The clinical diagnosis of an acute myocardial infarction was confirmed by electrocardiograms which showed an extensive anterior cardiac infarction involving the anteroseptal as well as the antero-lateral aspect of the myocardium and with extension through the septum (Fig. 1).

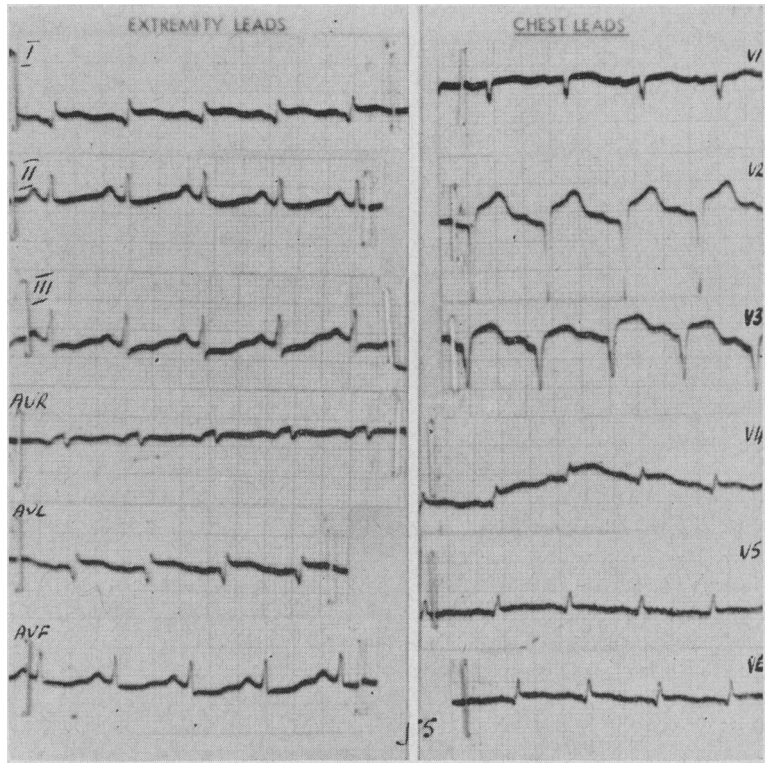

Fig. 1.—Electrocardiograms of Mrs. M.B. June 4.

A chest radiograph taken on June 5 showed clear costophrenic sinuses and a normal-sized heart. Urinalysis showed a trace of protein but was otherwise negative. The white cell count was 14,250, Hb. 84%, sedimentation rate 23 mm. in 1 hour. From the third day onward, the prothrombin time was maintained between 2 and 2½ times the control value by the use of dicoumarol. She was put on a 1,200 calorie diet.

On the third hospital day (June 6), she developed right and left heart failure with fine rales at the chest bases, cyanosis, extreme orthopnœa and œdema of both ankles as well as the sacrum. She was treated with digitalis, mercurial diuretics and low salt diet, which during the following two weeks controlled the failure and produced great symptomatic relief.

Levarterenol therapy had to be continued in varying concentrations for as long as three weeks. From June 4 to June 7, the patient's blood pressure was maintained by 1 ampoule of levarterenol at a rate of 6 to 8 drops per minute. It was noted that she suffered a drop in blood pressure at the slightest movement and that when she was simply turned to be washed, systolic pressure fell as much as 20 to 30 mm. Hg. On June 8, the rate of intravenous infusion with 1 ampoule of levarterenol had to be increased to 60 drops per minute in order to maintain the blood pressure, but in a few hours this failed to produce a systolic blood pressure of more than 80 mm. Hg and the levarterenol was increased to 2 ampoules. When she failed to show an adequate response after increasing the rate of flow to 60 drops per minute, an infusion of 3 ampoules was started. This again failed and she was given 4 ampoules, which at between 40 and 60 drops per minute maintained the blood pressure, until June 9 when it dropped to 60/40 and she went into shock. At that time she was started on a solution containing 5 ampoules of levarterenol, and at a rate of between 30 and 60 drops per minute her blood pressure rose and she improved considerably for several days. On June 11, we were again faced with a drop in blood pressure that did not respond to our maximum infusion rate (60 drops per minute) and the levarterenol was increased to 6 ampoules at a rate of between 40 and 60 drops per minute, at which her blood pressure was maintained. She was continued on the 6 ampoule strength solution until June 15 (except for one six-hour period during which time a seventh ampoule had to be added to the solution. After about 1,000 c.c. of this high concentration we were able to return to the 6 ampoule concentration). Over the next three or four days the strength of the solution was gradually decreased until by June 18 the patient was receiving 1 ampoule at a rate of 30 drops per minute. The drop rate was gradually reduced over the next week until 4 to 8 drops per minute of the 1 ampoule maintained her blood pressure. Several times the drip was stopped, but had to be restarted within a few minutes because of immediate blood pressure drop. It was noteworthy that this very weak concentration made such a great difference. However, by June 24, it could be permanently discontinued. A further 2,000 c.c. of 5% glucose in distilled water was given (in 12 hours) and then intravenous solutions were discontinued.

From the time we were able to stop the levarterenol, the patient made excellent progress. On June 27, she was taken completely out of oxygen. Her blood pressure at that time was 110/80 mm. Hg and her cardiac rate was 88 per minute and regular. There were no longer any signs of right or left heart failure. On July 24 she was allowed up, and ambulation gradually increased from then on. Her white cell count, sedimentation rate and urine were normal at this time, but her chest radiograph showed moderate left ventricular enlargement (with no pulmonary congestion). Although the persistent changes in the RS-T segments in the electrocardiograms (Fig. 2) suggest ventricular aneurysm, this was not confirmed by fluoroscopy. Her dicoumarol was gradually stopped and she was discharged on August 3 feeling well and able to walk the full length of the corridor without discomfort. She was last seen in the outpatient department in April 1956. She is able to do routine housework without discomfort and is living a fairly normal life. She is taking 0.25 mg. of digoxin daily and is on a low salt, low calorie diet.

DISCUSSION

There is no doubt that if 6 (and for a short period 7) ampoules of levarterenol per 1,000 c.c. had not been used, this patient would have died. This disproves the current opinion that if 4 ampoules per 1,000 c.c. does not raise the pressure there is no use in increasing the concentration. The maximum concentration given in this case (56 mcg. of levarterenol bitartrate) is almost twice the highest concentration reported in the literature.[4, 5]

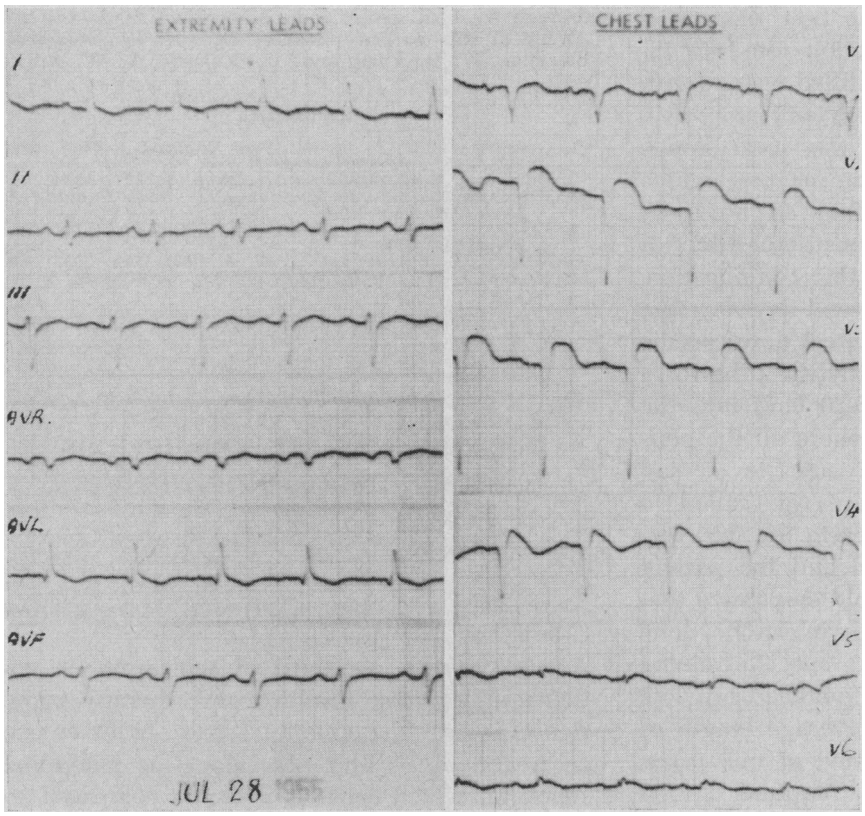

Fig. 2.—Electrocardiograms of Mrs. M.B. July 28.

This most impressive example (together with about 20 other cases of cardiac infarction that have been treated by us with Levophed) allows one to form certain conclusions not too clearly emphasized in the literature.

All agree that the longer the delay in instituting adequate levarterenol therapy, the less the chance of survival.[2] Therefore it is felt that one should not wait for the actual signs of shock, but if the systolic blood pressure remains under 95 mm. Hg (or under 100 in a known hypertensive) in spite of oxygen and morphine (or Demerol) for from one to three hours, this therapy should be started. If clinical evidence of peripheral vascular collapse is present (and not only a drop in blood pressure), it should be started immediately. A good rule is that if more than 60 drops per minute is necessary to maintain the systolic blood pressure as noted above, another ampoule of levarterenol should be added within 5 to 10 minutes. If the desired response is going to be obtained with a certain strength of solution, it is usually instantaneous, and much valuable time is lost if there is further delay before increasing the concentration.

The only satisfactory guide to dosage is the observation of the effect on the patient, and more particularly on the blood pressure. In most patients, 1 ampoule usually suffices, but in the more severe cases the concentration must be increased to 4 times before adequate blood pressure rise is obtained. It should not take more than 20 to 30 minutes to reach this concentration (which if required makes the prognosis worse). However, as this case demonstrates, one may have to give as much as 6 or 7 ampoules per 1,000 c.c., and still get recovery. (We must admit that in about half a dozen other patients given this high concentration there was no effect; in such cases where post-mortem was obtained, very extensive infarctions were found.) One of our patients, A.W., in heart failure and shock secondary to a cardiac infarction, had an excellent blood pressure response with 6 ampoules of levarterenol per 1,000 c.c., but one day later succumbed. Autopsy showed pulmonary congestion as well as a very extensive acute cardiac infarction. If heart failure is present, the drop rate should be reduced by increasing the concentration (e.g. 3 ampoules at the rate of 20 drops per minute rather than 1 ampoule at 60 drops per minute).

All patients on levarterenol therapy should have special nurses constantly present, as blood pressure should be taken every few minutes at first and then every 15 to 20 minutes for as long as this treatment is given. The doctor should explain to them in detail the mechanism and specific purpose of this therapy because, as time goes on, they must constantly increase or decrease the concentration, depending on the blood pressure response. Another need for constant observation is the danger of interstitial escape of levarterenol, which is very painful and may cause necrosis of tissue. Should that occur, the infusion should of course be immediately

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changed to another vein. The best therapy is immediate subcutaneous injection into the involved area of 10 to 20 c.c. distilled water (with 3 to 5 c.c. 2% procaine, which will stop pain immediately), thus diluting the levarterenol. This will usually prevent tissue necrosis, which may be very extensive (within 48 hours or sooner, due to the local vasoconstrictor effect of the drug[1]). To try to avoid this complication, it is wise in all cases where several days or more of therapy are contemplated, to cut down on the vein and insert a small polyethylene tube for a distance of 6 to 8 inches (15-20 cm.) into the vein. In several of our cases where all the peripheral veins were no longer suitable or had collapsed, our surgical confrere was called in to cut down on the femoral vein. In this way the therapy can be continued and the patient given renewed hope. One should emphasize that this latter procedure, although it can be done easily at the bedside, requires special training and should be performed by a qualified surgeon. Although 1 to 6 days is the average length of time the therapy is given, some of our cases, including the above example, required 2 to 3 weeks of therapy. Instead of stopping the intravenous drip as soon as the blood pressure is maintained without the levarterenol, one should immediately start an infusion of 1,000 c.c. of 5% dextrose in distilled water for a further period of 12 to 24 hours in case the pressure drops again (which it commonly does) so that levarterenol can be readministered without delay.

SUMMARY

A case is presented of extensive acute myocardial infarction with secondary shock (peripheral vascular collapse) as well as congestive heart failure. Levarterenol (Levophed) was given as part of the treatment. In order to maintain the blood pressure, the strength of Levophed solution had to be increased to a concentration of 7 ampoules per 1,000 c.c. (56 mcg. of levarterenol bitartrate). This is almost twice the highest concentration (with recovery) reported in the literature. This case demonstrates that stronger solutions of Levophed should be used if necessary and may be life-saving. Some other views on the use of levarterenol therapy are also presented.

The author wishes to take this opportunity to commend the nursing service of the Northwestern General Hospital together with the following staff physicians, who through their diligence and co-operation made the recovery of this patient possible: Drs. H. Kingstone, F. Brereton, W. B. Phair and, particularly, A. W. Brickenden.

REFERENCES

1. GREENWALD, H. P. *et al.*: *New England J. Med.*, **246**: 252, 1952.
2. GRIFFITH, G. C. *et al.*: *Circulation*, **9**: 527, 1954.
3. KURLAND, G. S. AND MALACH, M.: *New England J. Med.*, **247**: 383, 1952.
4. LIVESAY, W. R. AND CHAPMAN, D. W.: *Am. J. M. Sc.*, **225**: 159, 1953.
5. MILLER, A. J. *et al.*: *J. A. M. A.*, **152**: 1198, 1953.
6. MOYER, J. H. AND HANDLEY, C. A.: *Circulation*, **5**: 91, 1952.
7. VON EULER, U. S.: *Brit. M. J.*, **1**: 105, 1951.

SEVERE STATUS EPILEPTICUS DURING PROLONGED INSULIN COMA*

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APPROXIMATELY one-third of schizophrenic patients undergoing insulin coma therapy experience at least one epileptic seizure in the course of treatment.[1, 2] The percentage of individual shocks in which seizures occur as compared to the total number of shocks is considerably lower. It varies between 2, 5 and 7% in the material of different authors.[3, 4] This is an expression of the fact that patients have usually only one or very few seizures even during long-lasting treatments.

Status epilepticus during insulin coma treatment seems rare. Winkler mentions that he did not see a case of status epilepticus among 330 insulin treated patients, 115 of whom had epileptic seizures during treatment.[3] Von Braunmühl[5] observed 5 instances of "severe status epilepticus" among 566 patients treated with 40,000 insulin shocks; this is a frequency of 0.86% of cases, or 0.0125% of individual treatments. The dangerous nature of this complication, however, becomes clear from the figures given by Kinsey.[6] In his report on the incidence and cause of death in shock therapy, this author states that out of 12,234 insulin treated patients 90 died. Of the 90 deaths, 5 were due to status epilepticus and 38 to hypoglycæmic encephalopathy. Status epilepticus therefore accounts for 5.5% of the deaths, and protracted coma for 42.2%.

On the basis of these figures a status epilepticus during prolonged insulin coma might be

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